Pergamon

Tetrahedron 58 (2002) 5441–5452

TETRAHEDRON

Fast and efficient synthesis of novel fumagillin analogues

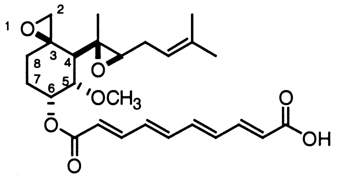
Jack E. Baldwin,* Paul G. Bulger and Rodolfo Marquez

Dyson Perrins Laboratory, Oxford University, South Parks Road, Oxford OX1 3QY, UK

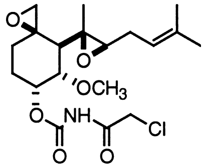
Received 18 March 2002; revised 23 April 2002; accepted 16 May 2002

Abstract—A novel class of non-carbocyclic ring analogues of the potent angiogenesis inhibitors fumagillin and TNP-470 have been enantioselectively and efficiently synthesised starting from pyridine-2-thiol in 10 steps in excellent overall yield. © 2002 Elsevier Science Ltd. All rights reserved.

Fumagillin **1**, isolated in 1951 by Elbe and Hanson from the microbial organism *Aspergillus fumigatus*, was originally described as an anti-microbial agent.[1] However, in 1990, Folkman and co-workers discovered that fumagillin potently and selectively inhibits angiogenesis (the growth of blood vessels).[2] Angiogenesis inhibitors are of great potential therapeutic use[3] and as a result of this discovery a considerable effort was made to explore the biological activity of fumagillin and its synthetic analogues.[4]



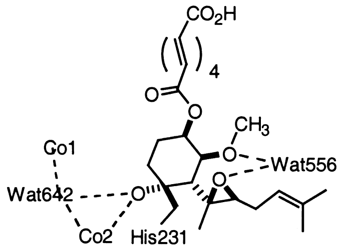
1



2

The compound TNP-470 **2**, a semi-synthetic derivative of fumagillin, has become one of the most promising small molecule cancer treatment candidates to date, and is currently in phase III clinical trials for the treatment of a variety of cancers.[5] Unfortunately, though more potent than fumagillin, TNP-470 has shown low half-life values, neurotoxic side effects (fatigue, vertigo, ataxia and loss of concentration) and possible disruption of normal angiogenic processes (female reproductive system, wound healing), which limit the available patient dosage.[6]

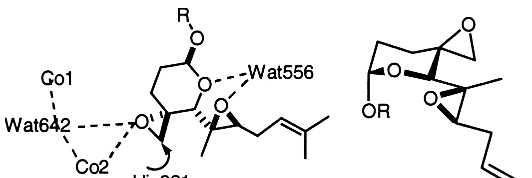
Fumagillin **1** and its analogues have been shown to bind very selectively to the protein methionine aminopeptidase type 2 (MetAP-2).[7] X-Ray crystal data has shown the mode of biological action to involve covalent bond formation by attack of the His231 residue in the MetAP-2 active site on the spiro epoxide of fumagillin, resulting in irreversible inhibition.[8]



Thus, based on an analysis of the reported biological data and structural studies, a series of novel ring oxygenated analogues have been designed and synthesised.

It was expected that replacing the methoxy-substituted C_5 atom with an oxygen atom would result in an increase in the rigidity of the cyclohexyl ring core, due to the anomeric effect at the C_6 position. This would possibly result in a better fit within the MetAP-2 active site, as the cyclohexyl ring in fumagillin appears to be somewhat flattened upon binding within the active site.

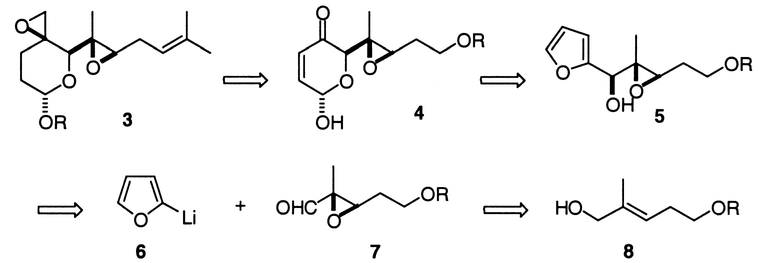
Furthermore, the introduced oxygen atom should also maintain the electrostatic interaction between the trisubstituted epoxide of the C_4 side-chain and the water556 molecule in the active site. It is believed that this interaction may play a crucial role in the correct orientation of the C_4 side-chain within the active site.



Keywords: fumagillin; TNP-470; angiogenesis inhibitors; analogues; furan rearrangement.

* Corresponding author. Tel.: +44-1865-275670; fax: +44-1865-275632; e-mail: jack.baldwin@chem.ox.ac.uk

0040–4020/02/$ - see front matter © 2002 Elsevier Science Ltd. All rights reserved.
PII: S0040-4020(02)00514-8



Scheme 1.

Herein we describe a fast and efficient synthesis of this new class of oxygenated fumagillin analogues, beginning with cheap and readily available starting materials.

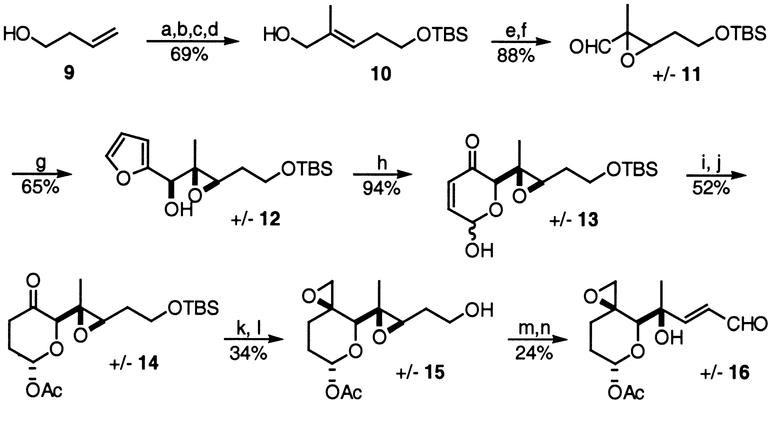
We proposed that the six-membered ring core could be constructed by the well-known oxidative rearrangement of furyl carbinol **5** to pyranone **4** (Scheme 1).[9] Appropriate functional-group transformations would then give the desired targets **3**. Furyl carbinol **5** could in turn be obtained by chelation-controlled addition of 2-furyllithium **6** to epoxy aldehyde **7**. Finally, the chiral epoxy aldehyde intermediate could be obtained by Sharpless epoxidation of allylic alcohol **8** (Scheme 1).

Our synthesis began with commercially available 3-buten-1-ol **9**, which was readily silyl protected and then ozonolysed to afford the desired aldehyde adduct (Scheme 2).[10] Wittig olefination, followed by ester reduction, generated the expected allylic alcohol **10** in good yield. Epoxidation of alcohol **10** under racemic conditions,[11] followed by Swern oxidation of the resulting epoxy alcohol intermediate afforded the corresponding aldehyde **11** in excellent yield for both steps.

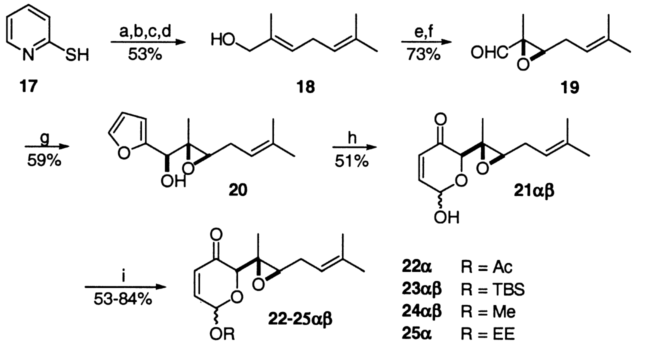
Alkylation of epoxy aldehyde **11** with 2-furyllithium proceeded cleanly to yield the desired secondary alcohol **12** in reasonable yield and as a 4:1 mixture of separable diastereomers at the newly formed stereocentre, with the main addition product being formed via a Cram chelation-controlled transition state. Treatment of alcohol **12** with *m*CPBA resulted in oxidative rearrangement to produce enone **13** with the correct stereochemistry at C_4 in good yield, and as a 1.5:1 mixture of diastereomers at the newly formed anomeric position.

With the six-membered ring core in place, we then turned our attention to the introduction of the required spiro epoxide functionality at C_3. Thus, protection of the anomeric hydroxyl group as the acetate, followed by catalytic hydrogenation of the enone double bond proceeded cleanly to afford the desired ketone **14** in good yield. However, conversion of ketone **14** into the spiro epoxide **15** proved to be extremely challenging, as previously reported epoxidation conditions[12] were met with a complete lack of success. It was not until the epoxidation was attempted using the highly nucleophilic bromomethyllithium,[13] generated in situ, that the desired spiro epoxide was obtained. Although the yield was only moderate, most likely due to competing attack of the bromomethyl anion on the acetate group, the product was formed as a single diastereomer, with the initial attack being on the less hindered face of the ketone.

Removal of the silyl protecting group afforded alcohol **15**, which was then oxidised to the corresponding aldehyde. However, olefination of the aldehyde failed to produce any of the desired alkene, instead yielding enal **16** as the sole product, which arose as a result of β-elimination of the side-chain epoxide rather than olefination. This elimination, while easily explained, was nevertheless extremely disappointing, considering previous reports that indicated that such an olefination, as was used in a total synthesis of fumagillin itself,[12] would be successful.



Scheme 2. *Reagents and conditions*: (a) TBSCl, Imid.; (b) O_3, DMS; (c) $PPh_3C(Me)CO_2Et$; (d) Dibal-H; (e) $VO(acac)_2$, TBHP; (f) Swern; (g) furan, *n*BuLi, then **11**; (h) *m*CPBA; (i) Ac_2O; Py; (j) H_2, Pd/C; (k) CH_2Br_2, *n*BuLi; (l) TBAF; (m) Swern; (n) NaH, $(CH_3)_2CHPPh_3Br$.



Scheme 3. *Reagents and conditions*: (a) 3-chloro-2-methyl-propene, NaOEt; (b) prenyl bromide, *n*BuLi; (c) *m*CPBA; (d)Et_2NH; (e) D-(−)-DIPT, $Ti(O^iPr)_4$, TBHP; (f) Swern; (g) furan, *n*BuLi, then **19**; (g) $VO(acac)_2$, TBHP; (h) RX, base or ethylvinyl ether, PPTS.

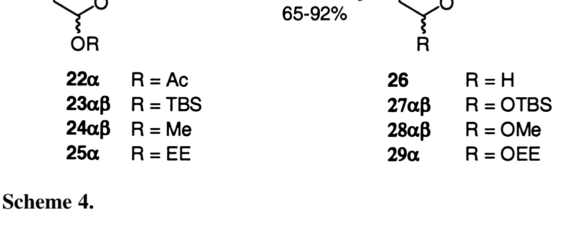
The inability to prevent this elimination from occurring in the last step of this route prompted us to modify our approach, namely to introduce the complete side chain at the beginning of the synthetic sequence.

The modified approach (Scheme 3) began with commercially available 2-mercaptopyridine **17** which, following the procedure of Mori and Ueda,[14] was converted in four steps in good yield to the unconjugated dienol **18**. Sharpless epoxidation followed by Swern oxidation gave epoxy aldehyde **19** in good yield and excellent enantiomeric excess (ee>98%).[15]

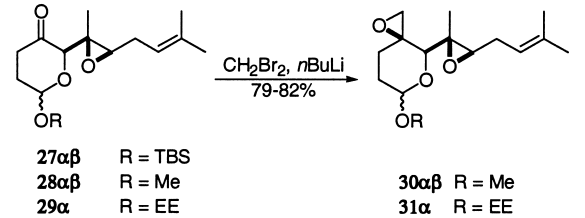
Addition of 2-furyllithium again proceeded cleanly to yield the secondary alcohol as a 3.5:1 mixture of diastereomers, with the desired product **20** being isolated in 59% yield after chromatographic separation. Oxidative rearrangement of the furan ring was first attempted using *m*CPBA as before, but this led to preferential epoxidation of the trisubstituted double bond. However, treatment of furan **20** under hydroxyl-directed epoxidation conditions ($VO(acac)_2$/*t*-butylhydroperoxide)[11] produced the desired enone **21** in reasonable yield and as a 1.5:1 mixture of diastereomers at the anomeric position.

A variety of protecting groups were then investigated for the protection of the anomeric hydroxyl group, with protection as the acetate ester and the TBS, methyl and ethoxyethyl ethyl ethers under standard conditions to afford the desired protected hemiketals **22–25** in good yields.

Chemoselective reduction of the enone double bond in hemiketals **22–25** was then performed (Scheme 4). Catalytic hydrogenation was unsatisfactory, as the side chain double bond was reduced preferentially, and it was only after considerable experimentation that the appropriate conditions were found, namely the use of Raney-Nickel in THF.[16] However, while the silyl **23**, methyl **24** and ethoxyethyl **25** protected lactols produced the desired saturated ketones **27–29**, acetate **22** underwent concomitant hydrogenolysis to afford pyran **26** as the sole product.



Scheme 4.

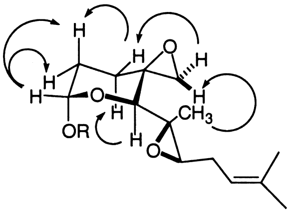


Scheme 5.

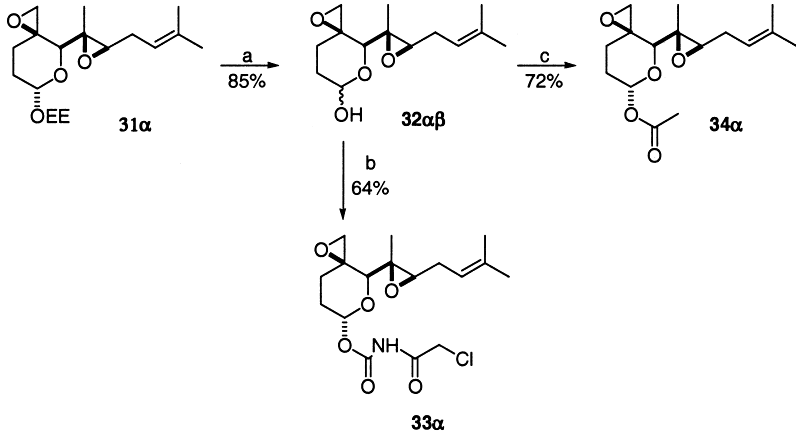
Epoxidation of ketones **27–29** was again only possible using bromomethyllithium, and with mixed results (Scheme 5). Thus, while the methyl **28** and ethoxyethyl **29** protected compounds were cleanly converted into spiro epoxides **30** and **31** in good yield and as single diastereomers at the newly formed stereocentre, silyl ether **27** failed to undergo any reaction, and most of the starting material could invariably be recovered unchanged.

The final steps of the synthesis were then deprotection followed by acylation of the anomeric hydroxyl group. Unfortunately, hydrolysis of the methyl ether protecting group under a variety of conditions proved unsuccessful in both the **30α** and **30β** anomeric series. However treatment of compound **31** with PPTS in acetone/water (4:1 v/v) at 45°C resulted in clean removal of the ethoxyethyl group, forming lactol **32** in excellent yield (Scheme 6).

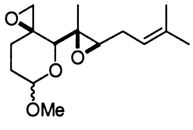
Once synthesised, the key lactol **32** allowed us to easily install various side chains at the C_6 position by simple acylation. Thus, treatment of lactol **32** with chloroacetyl isocyanate or acetic anhydride generated the desired carbamate and acetate analogues **33** and **34**, respectively (α/β ratios typically >10:1). The absolute stereochemistry of the final products was confirmed through nOe analysis.



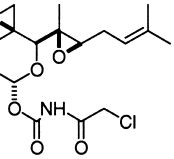
In conclusion, we have rapidly and efficiently completed the enantioselective synthesis of the first non-carbocyclic analogues of fumagillin and TNP-470 in ten flexible and easily modifiable steps staring from commercially available 2-mercaptopyridine. We hope that this novel class of compounds will shed further light into the mechanism of fumagillin's anti-angiogenic activity, while at the same time addressing some of the toxicity side effects.



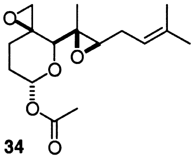
Scheme 6. *Reagents and conditions*: (a) PPTS, acetone, water; (b) $ClCH_2COCNO$; (c) Ac_2O, Py.



30αβ



33



34

The carbamate **33**, acetate **34** and both α- and β-methoxy analogues **30α** and **30β** analogues have been submitted for biological testing and the results will be reported shortly.

1. Experimental

1.1. General methods

^1H NMR spectra were recorded on Bruker DPX250 (250 MHz), DPX400 (400 MHz), DRX500 (500 MHz) or AMX500 (500 MHz) spectrometers. ^{13}C NMR spectra were recorded on Bruker DPX250 (63 MHz), DPX400 (100 MHz) or AMX500 (125 MHz). Chemical shifts (δ) are reported in ppm, and are referenced to the residual solvent peak. Coupling constants (J) are quoted to the nearest 0.1 Hz.

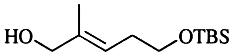
IR spectra were recorded as a thin film between NaCl plates on a Perkin–Elmer 1750 FTIR spectrometer. Only selected peaks are reported, absorption maxima being recorded in cm^{-1}.

Low-resolution mass spectra (m/z) were recorded on V. G. Masslab (CI), Micromass Platform 1 (APCI) or V. G. Trio 1 (GCMS) spectrometers. m/z values of major peaks are reported in Daltons, with intensities quoted as percentages of the base peak. High-resolution mass spectra were recorded on a V. G. Autospec chemical ionisation mass spectrometer.

TLC was performed on Merck aluminium foil-backed sheets precoated with 0.2 mm Kieselgel 60 F_{254}. Product spots were visualised by the quenching of UV fluorescence (λ_{max}, 254 nm), or by staining with a solution of 5% (w/v) *dodeca*molybdophosphoric acid in EtOH followed by heating. Flash column chromatography was performed using silica gel (Sorbisil™ C_{60} 40–60 μm).

All reactions were performed in oven-dried (24 h at 110°C) glassware under inert (Ar or N_2) atmosphere. Anhydrous THF and Et_2O were obtained by distillation from sodium benzophenone ketyl under N_2. Anhydrous DCM was obtained by distillation from CaH_2 under N_2. '40/60 Petrol' refers to that fraction of light petroleum ether boiling at 40–60°C and was distilled before use.

1.2. Experimental procedures

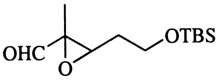


1.2.1. (2*E*)-2-Methyl-5-[((1,1-dimethyl)ethyl)dimethylsilylsilyloxy] pent-2-en-1-ol (10). To a stirred solution of 3-buten-1-ol (4.93 g, 68.4 mmol, 1.0 equiv.) in dry DCM (70 ml) was added imidazole (5.12 g, 75.2 mmol, 1.1 equiv.) and TBSCl (11.7 g, 75.2 mmol, 1.1 equiv.) at rt. After 90 min, the mixture was partitioned between Et_2O (200 ml) and H_2O (100 ml). The organic layer was washed with 10% HCl (70 ml), brine (70 ml), dried ($MgSO_4$), filtered and concentrated to afford the crude silyl ether (13.23 g) as a colourless oil, which was used without further purification in the next step.

Ozone was bubbled through a solution of the crude silyl ether (13.23 g) in DCM (80 ml) at −78°C until a pale blue colour developed. Oxygen was bubbled through the solution for 5 min to remove the excess ozone, followed by argon for another 5 min. Dimethyl sulphide (200 ml) was added, and the mixture was allowed to warm to rt and stirred for 24 h. The mixture was concentrated, then partitioned between Et_2O (150 ml) and H_2O (150 ml). The aqueous layer was extracted with Et_2O (2×100 ml), and the combined organic layers were washed with brine (100 ml), dried ($MgSO_4$), filtered and concentrated to afford the aldehyde[14] (12.75 g) as a colourless oil which was used without further purification in the next step.

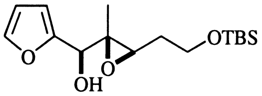
To a stirred solution of the crude aldehyde (12.75 g) in toluene (230 ml) was added (1-ethoxycarbonylethylidene)triphenylphosphorane (25 g, 69 mmol, ca. 1.0 equiv.) in one portion at rt. The mixture was refluxed for 18 h, then cooled to rt and concentrated. The residue was dissolved in hexane (200 ml), and the precipitated triphenylphosphine oxide filtered off. The filtrate was then concentrated. Purification by flash column chromatography (47:3 30/40 petrol/Et_2O) gave ethyl (2*E*)-2-methyl-5-[((1,1-dimethyl)ethyl)dimethylsilyloxy]pent-2-enoate (13.43 g, 72%) as a colourless oil: R_f 0.24 (47:3 30/40 petrol/Et_2O); ν_{max}(film) (cm^{-1}) 2956, 2859, 1714, 1653, 1472, 1257, 837; δ_H(400 MHz; $CDCl_3$) 0.04 (6H, s), 0.88 (9H, s), 1.27 (3H, t, J=7.1 Hz), 1.83 (3H, d, J=0.9 Hz), 2.35–2.40 (2H, m), 3.69 (2H, t, J=6.7 Hz), 4.17 (2H, t, J=7.1 Hz), 6.72–6.76 (1H, m); δ_C(100 MHz; $CDCl_3$) −5.38, 12.48, 14.21, 18.25, 25.83, 32.32, 60.34, 61.68, 129.18, 138.45, 167.99; *m/z* (GCMS) 290 (95%, MNH_4^+), 273 (100, MH^+), 215 (42), 141 (31); HRMS: Found 273.1886 (MH^+). $C_{14}H_{29}O_3Si$ requires 273.1886.

To a stirred solution of the ester (1.074 g, 3.9 mmol, 1.0 equiv.) in dry Et_2O (20 ml) at −78°C was added Dibal (7.8 ml of a 1.5 M solution in toluene, 11.7 mmol, 3.0 equiv.) dropwise over 5 min. The mixture was stirred at −78°C for 1 h, then at 0°C for 1 h, then quenched by the cautious addition of MeOH (5 ml). 3 M Sodium potassium tartrate tetrahydrate (50 ml) was added, and the mixture stirred for 3 h. The layers were separated, and the aqueous layer extracted with EtOAc (3×30 ml). The combined organic layers were washed with brine (50 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (3:2 30/40 petrol/Et_2O) gave the title compound (0.87 g, 96%) as a colourless oil: R_f 0.31 (3:2 30/40 petrol/Et_2O); ν_{max}(film)/cm^{-1} 3350, 2897, 2858, 1671, 1473, 1256, 1095; δ_H(400 MHz; $CDCl_3$) 0.06 (6H, s), 0.89 (9H, s), 1.68 (3H, s), 2.24–2.30 (2H, m), 3.60 (2H, t, J=7.0 Hz), 3.99 (1H, br s), 5.38–5.40 (1H, m); δ_C(100 MHz; $CDCl_3$) −5.41, 13.75, 18.33, 25.91, 31.40, 62.71, 68.77, 122.05, 136.59; *m/z* (CI^+) 248 (28%, MNH_4^+), 231 (27, MH^+), 213 (100), 132 (24), 99 (25).

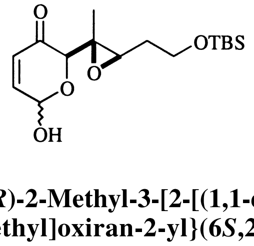


1.2.2. (±)-{(2*S*,3*R*)-3-[2-[((1,1-Dimethyl)ethyl)dimethylsilyloxy)ethyl] oxiran-2-methyloxirane-2-carbaldehyde (11). To a stirred solution of alcohol (**10**) (0.4 g, 1.74 mmol, 1.0 equiv.) in benzene (15 ml) was added $VO(acac)_2$ (18 mg, 0.05 mmol, 0.03 equiv.) then *tert*-butylhydroperoxide (0.42 ml of a 5 M solution in decane, 2.08 mmol, 1.2 equiv.) at rt. After 3 h more *tert*-butylhydroperoxide (0.1 ml) was added. After another 2 h, the mixture was concentrated. The residue was dissolved in Et_2O, filtered through a pad of Florisil, and concentrated. Purification by flash column chromatography (1:1 30/40 petrol/Et_2O) gave (±)-{(2*S*,3*R*)-2-methyl-3-[2-[((1,1-dimethyl)ethyl)dimethylsilyloxy)ethyl]oxiran-2-yl}methan-1-ol (0.41 g, 96%) as a colourless oil: R_f 0.32 (1:1 30/40 petrol/Et_2O); ν_{max}(film)/cm^{-1} 3436, 2930, 1472, 1256, 1098, 836; δ_H(400 MHz; $CDCl_3$) 0.06 (6H, s), 0.89 (9H, s), 1.29 (3H, s), 1.74–1.83 (2H, m), 1.97 (1H, dd, J=8.4, 4.7 Hz), 3.16 (1H, t, J=6.3 Hz), 3.56 (1H, dd, J=12.2, 8.4 Hz), 3.69 (1H, dd, J=12.2, 4.7 Hz), 3.76–3.80 (2H, m); δ_C(63 MHz; $CDCl_3$) −5.06, 14.69, 18.63, 26.25, 31.95, 58.40, 60.70, 61.57, 66.02; *m/z* (CI) 264 (18%, MNH_4^+), 247 (96, MH^+), 229 (100), 189 (65), 171 (34), 97 (58).

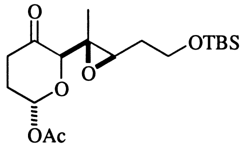
To a stirred solution of oxalyl chloride (1.46 ml, 16.7 mmol, 2.0 equiv.) in dry DCM (30 ml) was added a solution of DMSO (2.4 ml, 33.4 mmol, 4.0 equiv.) in dry DCM (5 ml) dropwise at −78°C. After 10 min a solution of the epoxy alcohol (2.06 g, 8.35 mmol, 1.0 equiv.) in dry DCM (10 ml) was added dropwise. After 20 min Et_3N (9.3 ml, 66.8 mmol, 8.0 equiv.) was added, and the mixture allowed to warm to rt. After 1 h the mixture was poured into H_2O (50 ml). The aqueous layer was extracted with DCM (2×40 ml), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (6:1 40/60 petrol/Et_2O) gave the title compound (1.877 g, 92%) as a colourless oil: R_f 0.55 (1:1 40/60 petrol/Et_2O); ν_{max}(film)/cm^{-1} 2957, 2931, 1732, 1472, 1257, 1099, 837; δ_H(500 MHz; $CDCl_3$) 0.07 (6H, s), 0.89 (9H, s), 1.41 (3H, s), 1.81–1.91 (2H, m), 3.32 (1H, t, J=5.8 Hz), 3.82 (2H, dd, J=6.9, 5.1 Hz), 8.87 (1H, s); δ_C(126 MHz; $CDCl_3$) −5.56, 10.11, 18.13 25.73, 31.13, 57.76, 59.85, 62.02, 199.94; *m/z* (GCMS) 246 (100%, MH^+), 229 (79), 171 (57), 83 (65); HRMS: Found 247.1737 (MH^+). $C_{12}H_{27}O_3Si$ requires 247.1729.



1.2.3. (±)-(1*R*){(2*R*,3*R*)-2-Methyl-3-[2-[((1,1-dimethyl)ethyl)dimethylsilyloxy]ethyl]oxiran-2-yl}-22-furylmethan-1-ol (12). To a stirred solution of furan (freshly distilled from $CaCO_3$, 0.64 ml, 8.83 mmol, 1.3 equiv.) in dry THF (40 ml) was added *n*BuLi (3.8 ml of a 2.33 M solution in hexane, 8.83 mmol, 1.3 equiv.) dropwise at −78°C. The mixture was stirred at −78°C for 20 min, at −5°C for 3 h, at rt for 10 min, and was then recooled to −78°C before a solution of aldehyde (**11**) (1.66 g, 6.79 mmol, 1.0 equiv.) in dry THF (8 ml) was added dropwise. The mixture was stirred at −78°C for 2 h then allowed to warm to rt overnight. The mixture was quenched with sat. aq. NH_4Cl (50 ml). The layers were separated, and the aqueous layer extracted with Et_2O (3×30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. ^1H NMR analysis of the crude product mixture indicated a 4:1 mixture of diastereomers. Purification by flash column chromatography (23:2 DCM:EtOAc) gave the title compound (1.389 g, 65%) as a pale yellow oil: R_f 0.29 (23:2 DCM:EtOAc); ν_{max}(film)/cm^{-1} 3436, 2885, 1472, 1257, 1097, 835; δ_H(400 MHz; $CDCl_3$) 0.07 (6H, s), 0.90 (9H, s), 1.24 (3H, s), 1.76–1.86 (2H, m), 2.60 (1H, d, J=6.8 Hz), 3.27 (1H, dd, J=6.7, 5.6 Hz), 3.79 (1H, m), 4.49 (1H, d, J=6.7 Hz), 6.34–6.36 (2H, m), 7.39 (1H, m); δ_C(100 MHz; $CDCl_3$) 12.85, 18.30, 25.89, 31.62, 58.22, 60.27, 62.24, 71.58, 107.26, 110.22, 142.19, 153.37.

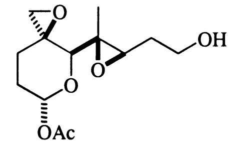


1.2.4. (±)-2-{(3*R*)-2-Methyl-3-[2-[(1,1-dimethyl)ethyldimethylsilyloxy]ethyl]oxiran-2-yl}(6*S*,2*R*)-6-hydroxy-6-hydro-2*H*-pyran-3-one (13). To a stirred solution of furan (**12**) (1.382 g, 4.42 mmol, 1.0 equiv.) in dry DCM (35 ml) was added *m*CPBA (55% purity, 1.526 g, 4.87 mmol, 1.1 equiv.) in one portion at 0°C. The mixture was allowed to warm to rt over 22 h, then partitioned between 50% sat. aq. $Na_2S_2O_3$ (60 ml) and DCM (40 ml). The layers were separated, and the organic layer was washed with sat. aq. $NaHCO_3$ (40 ml). The combined aqueous layers were extracted with DCM (3×40 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford the crude product (1.36 g, 94%) as a pale yellow oil and as a 1:1.5 mixture of anomers. This material was used without further purification in the next step: R_f 0.27 (21:4 DCM:EtOAc).



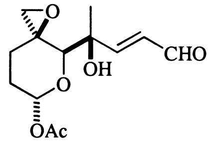
1.2.5. (±)-6-{(3*R*)-2-Methyl-3-[2-[((1,1-dimethyl)ethyl)-dimethylsilyloxy]ethyl]oxiran-2-yl}(2*R*,6*R*)-5-oxo-3,4,6-trihydro-2*H*-pyran-2-yl acetate (14). To a stirred solution of pyranone (**13**) (80 mg, 0.24 mmol, 1.0 equiv.) in dry DCM (6 ml) was added pyridine (160 μl, 1.95 mmol, 8.0 equiv.), acetic anhydride (110 μl, 1.22 mmol, 5.0 equiv.) and DMAP (45 mg) at 0°C. After 90 min H_2O (10 ml) was added. The layers were separated, and the aqueous layer extracted with DCM (3×10 ml). The combined organic layers were washed with brine (1×20 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (27:23 40/60 petrol/Et_2O) gave (±)-6-{(3*R*)-2-methyl-3-[2-[((1,1,-dimethyl)ethyl)dimethylsilyloxy] ethyl]oxiran-2-yl}(2*R*,6*R*)-5-oxo-6-hydro-2*H*-pyran-2-yl acetate (55 mg, 61%) as a pale yellow oil: R_f 0.27 (1:1 40/60 petrol/Et_2O); ν_{max}(film)/cm^{-1} 2956, 2868, 1759, 1699, 1462, 1213, 1100; δ_H(400 MHz; $CDCl_3$) 0.09 (6H, s), 0.91 (9H, s), 1.27 (3H, s), 1.71–1.80 (1H, m), 1.90–1.99 (1H, m), 2.13 (3H, s), 3.14 (1H, dd, J=7.2, 5.1 Hz), 3.81–3.88 (2H, m), 4.13 (1H, s), 6.23 (1H, d, J=10.3 Hz), 6.60 (1H, d, J=3.7 Hz), 6.94 (1H, dd, J=10.3, 3.7 Hz); δ_C(100 MHz; $CDCl_3$) −5.38, 12.36, 18.27, 20.92, 25.88, 31.38, 58.56, 59.67, 60.11, 81.78, 86.73, 128.44, 142.18, 169.28, 192.46; *m/z* (CI) 311 (100%, $[M-OAc]^+$), 293 (46), 253 (61).

To a solution of the acetate (51 mg, 0.14 mmol, 1.0 equiv.) in EtOAc (6 ml) was added 10% Pd/C (15 mg). The mixture was degassed and flushed with H_2 three times, then placed under H_2 (balloon) and stirred for 22 h. The mixture was filtered through Celite, and the filtrate concentrated. Purification by flash column chromatography (27:23 40/60 petrol/Et_2O) gave the title compound (43 mg, 86%) as a colourless oil: R_f 0.23 (27:23 40/60 petrol/Et_2O); ν_{max}(film)/cm^{-1} 2957, 1750, 1472, 1224, 1098, 836; δ_H(400 MHz; $CDCl_3$) 0.07 (6H, s), 0.89 (9H, s), 1.25 (3H, s), 1.69–1.74 (1H, m),1.86–1.91 (1H, m), 2.06–2.10 (1H, m), 1.90 (3H, s), 2.42–2.47 (1H, m), 2.52–2.57 (2H, m), 3.12 (1H, dd, J=7.1, 5.1 Hz), 3.78–3.82 (2H, m), 3.91 (1H, s), 6.37 (1H, t, J=4.7 Hz); δ_C(400 MHz; $CDCl_3$) −5.40, 12.86, 18.29, 21.14, 25.76, 25.90, 27.23, 31.39, 33.58, 58.03, 59.60, 60.16, 82.00, 90.56, 169.40, 206.01; *m/z* (CI) 390 (28, MNH_4^+), 373 (8, MH^+), 355 (67), 313 (100), 295 (66), 181 (52); HRMS: Found 395.1864 (MNa^+). $C_{18}H_{32}O_6{}^{23}NaSi$ requires 395.1866.



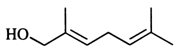
1.2.6. (±)-4-[(3*R*)-3-(2-Hydroxyethyl)-2-methyloxiran-2-yl](3*S*,4*S*,6*R*)-1,5-dioxaspiro[2.5]oct-6-yl acetate (15). To a stirred solution of ketone (**14**) (68 mg, 0.18 mmol, 1.0 equiv.) and dibromomethane (15 μl, 0.22 mmol, 1.2 equiv.) in dry THF (2 ml) was added *n*BuLi (84 μl of a 2.32 M solution in hexanes, 0.19 mmol, 1.05 equiv.) dropwise at −78°C. The mixture was allowed to warm to rt, and stirred for 18 h. The mixture was partitioned between Et_2O (10 ml) and sat. aq. NH_4Cl (10 ml). The aqueous layer was extracted with Et_2O (3×10 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (14:11 40/60 petrol/Et_2O) gave (±)-4-[(3*R*)-3-[2-[((1,1-dimethyl)ethyl)dimethylsilyloxy]ethyl]-2-methyloxiran-2-yl]-(3*S*,4*S*,6*R*)-1,5-dioxaspiro[2.5]oct-6-yl acetate (30 mg, 42%) as a pale yellow oil: R_f 0.16 (3:2 40/60 petrol/Et_2O); ν_{max}(film)/cm^{-1} 2955, 1749, 1372, 1204, 1096; δ_H(400 MHz; $CDCl_3$) 0.08 (6H, s), 0.91 (9H, s), 1.25–1.32 (1H, m), 1.29 (3H, s), 1.71–1.79 (2H, m), 1.86 (1H, dt, J=13.9, 1.6 Hz), 2.10 (3H, s), 2.22–2.27 (1H, m), 2.34–2.39 (1H, m), 2.56 (1H, d, J=4.3 Hz), 2.86 (1H, t, J=6.0 Hz), 3.02 (1H, d, J=4.3 Hz), 3.76 (1H, s), 3.77–3.80 (2H, m), 6.35 (1H, s); δ_C(100 MHz; $CDCl_3$) 12.79, 18.29, 21.24, 25.88, 26.37, 26.92, 31.25, 50.34, 56.02, 58.45, 59.30, 60.18, 78.39, 91.93, 125.50, 169.40; *m/z* (CI) 404 (4%, MNH_4^+), 387 (3, MH^+), 309 (100), 195 (47), 165 (50), 95 (57).

To a stirred solution of the spiro epoxide (80 mg, 0.21 mmol, 1.0 equiv.) in dry THF (4 ml) was added TBAF (0.25 ml of a 1 M solution in THF, 0.25 mmol, 1.2 equiv.) dropwise at rt. After 1 h more TBAF (0.1 ml) was added. After another 90 min, the mixture was partitioned between EtOAc (10 ml) and H_2O (10 ml). The aqueous layer was extracted with EtOAc (3×10 ml). The combined organic layers were washed with brine (1×10 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (EtOAc) gave the title compound (45 mg, 80%) as a colourless oil: R_f 0.22 (EtOAc); ν_{max}(film)/cm^{-1} 3462, 2936, 1748, 1205, 1010; δ_H(250 MHz; $CDCl_3$) 1.31 (3H, s), 1.78–1.89 (3H, m), 2.09 (3H, s), 2.16–2.33 (3H, m), 2.62 (1H, d, J=4.2 Hz), 2.90 (1H, t, J=5.8 Hz), 2.94 (1H, d, J=4.2 Hz), 3.75 (1H, s), 3.80–3.86 (2H, m), 6.33–6.35 (1H, m); δ_C(63 MHz,$CDCl_3$) 13.26, 21.62, 26.73, 27.37, 30.81, 50.97, 56.57, 58.99, 59.75, 60.45, 78.55, 92.23, 169.89; *m/z* (CI) 290 (31%, MNH_4^+), 255 (19), 230 (36), 213 (80), 195 (94), 183 (100), 123 (98); HRMS: Found: 295.1166 (MNa^+). $C_{13}H_{20}O_6{}^{23}Na$ requires 295.1158.



1.2.7. (±)-4-((2*E*)-1-Hydroxy-1-methyl-4-oxobut-2-enyl)-(3*S*,4*R*,6*R*)-1,5-dioxaspiro[2.5]oct-6-yl acetate (16). To a stirred solution of oxalyl chloride (49 μl, 0.56 mmol, 4.0 equiv.) in dry DCM (3 ml) was added a solution of DMSO (74 μl, 1.12 mmol, 8.0 equiv.) in dry DCM (1 ml) dropwise at −78°C. After 10 min a solution of alcohol (**15**) (38 mg, 0.14 mmol, 1.0 equiv.) in dry DCM (1 ml) was added dropwise. After 20 min Et_3N (0.31 ml, 2.24 mmol, 16.0 equiv.) was added, and the mixture allowed to warm to rt. After 1 h the mixture was poured into H_2O (50 ml). The aqueous layer was extracted with DCM (2×40 ml), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated to afford the crude product as a colourless oil, which was used without further purification in the next step.

*n*BuLi (67 μl of a 2.3 M solution in hexanes, 0.15 mmol, 1.1 equiv.) was added to a suspension of isopropyltriphenylphosphonium iodide (73 mg, 0.17 mmol, 1.2 equiv.) in dry THF (3 ml) at 0°C. After 15 min the mixture was cooled to −78°C, and a solution of the crude aldehyde in dry THF (2 ml) was added dropwise. The mixture was stirred at −78°C for 1 h then at 0°C for 2 h. The mixture was partitioned between EtOAc (10 ml) and H_2O (10 ml). The aqueous layer was extracted with EtOAc (3×10 ml), and the combined organic layers were washed with brine (1×10 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (1:4 40/60 petrol/Et_2O) gave the title compound (9 mg, 24%) as a yellow oil: R_f 0.17 (1:4 40/60 petrol/Et_2O); δ_H(500 MHz; $CDCl_3$) 1.43 (3H, s), 1.61–1.64 (1H, m), 1.83–1.87 (1H, m), 1.96–2.00 (1H, m), 2.18 (3H, s), 2.33–2.39 (1H, m), 2.68 (1H, d, *J*=5.0 Hz), 3.20 (1H, d, *J*=5.0 Hz), 4.13 (1H, s), 6.32 (1H, m), 6.37 (1H, dd, *J*=16.0, 7.5 Hz), 7.14 (1H, d, *J*=16.0 Hz), 9.66 (1H, d, *J*=7.5 Hz); δ_C(125 MHz; $CDCl_3$) 21.5, 27.5, 27.5, 27.8, 30.8, 53.5, 58.2, 74.9, 76.1, 92.0, 129.6, 160.2, 194.4. Sample decomposed before IR, *m*/*z* and HRMS could be recorded.

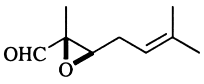


1.2.8. (5*Z*,2*E*)-2,6-Dimethylhepta-2,5-dien-1-ol (18).[14]

Freshly cut sodium (11.26 g, 0.49 mol, 1.05 equiv.) was slowly added to absolute EtOH (600 ml) at 0°C. Once all the sodium had dissolved, 2-mercaptopyridine (**17**) (51.84 g, 0.47 mol, 1.0 equiv.) was added in one portion at 0°C. After 10 min 3-chloro-2-methylpropene (53 ml, 0.54 mol, 1.15 equiv.) was added. After 3 h the mixture was concentrated; the residue was partitioned between Et_2O (300 ml) and H_2O (300 ml). The aqueous layer was extracted with Et_2O (3×200 ml), and the combined organic layers were washed with 5% aq. NaOH, brine, dried ($MgSO_4$), filtered and concentrated. Purification by vacuum distillation gave 2-(2-methylprop-2-enylthio)pyridine (73.12 g, 95%) as a yellow oil: R_f 0.37 (7:1 40/60 petrol/EtOAc); bp 84–87°C/0.9 mmHg (lit.[14] 90–92°C/1 mmHg); δ_H(250 MHz; $CDCl_3$) 1.88 (3H, t, *J*=1.1 Hz), 3.88 (2H, d, *J*=0.9 Hz), 4.89 (1H, m), 5.05 (1H, m), 7.00 (1H, ddd, *J*=8.2, 7.2, 1.0 Hz), 7.22 (1H, dt, *J*=8.2, 1.0 Hz), 7.50 (1H, m), 8.47 (1H, ddd, *J*=5.0, 1.9, 1.0 Hz).

To a stirred solution of the sulphide (73.7 g, 0.45 mol, 1.0 equiv.) in dry THF (500 ml) was added *n*BuLi (190 ml of a 2.5 M solution in hexanes, 0.48 mol, 1.07 equiv.) dropwise at −45°C (dry ice/MeCN). After 30 min the mixture was cooled to −78°C and 4-bromo-2-methyl-2-butene (55.5 ml, 0.48 mol, 1.08 equiv.) added dropwise. The mixture was stirred at −78°C for 1 h, −45°C for 1 h, then allowed to warm to rt over 3 h. The reaction was quenched with sat. aq. NH_4Cl (400 ml). The layers were separated, and the aqueous layer extracted with Et_2O (3×300 ml). The combined organic layers were washed with brine (1×300 ml), dried ($MgSO_4$), filtered and concentrated. Purification by vacuum distillation gave 2-[(3*Z*)-4-Methyl-1-(1-methylvinyl)pent-3-enylthio]pyridine (80.4 g, 76%) as a pale yellow oil: R_f 0.3 (13:1 40/60 petrol/Et_2O); bp 125–130°C/1.1 mmHg (lit.[14] 110–120/1 mmHg); δ_H(500 MHz; $CDCl_3$) 1.70 (3H, s), 1.74 (3H, d, *J*=1.0 Hz), 1.88 (3H, s), 2.27–2.52 (1H, m), 2.58–2.63 (1H, m), 4.46 (1H, dd, *J*=9.0 and 6.5 Hz), 4.90 (1H, q, *J*=1.0 Hz), 5.04 (1H, s), 5.20 (1H, m), 7.02 (1H, ddd, *J*=8.0, 5.0, 0.5 Hz), 7.22 (1H, d, *J*=8.0 Hz), 7.51 (1H, app dt, *J*=8.0, 8.0, 1.5 Hz), 8.48 (1H, ddd, *J*=5.0, 1.5, 0.5 Hz).

To a stirred solution of the sulphide (16.18 g, 69.3 mmol, 1.0 equiv.) in DCM was added a solution of *m*CPBA (77% purity, 16.3 g, 72.8 mmol, 1.05 equiv.) in DCM (300 ml) over 1 h at −25°C. The mixture was allowed to warm to rt over 3 h. The mixture was washed with sat. aq. Na_2CO_3 (500 ml). The aqueous layer was extracted with DCM (2×300 ml), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. The residue was dissolved in MeOH (150 ml), and diethylamine (150 ml) was added in one portion at rt. After 20 h the mixture was concentrated, and the residue partitioned between Et_2O (200 ml) and H_2O (200 ml). The aqueous layer was extracted with Et_2O (3×150 ml), and the combined organic layers were washed with 2 M HCl (2×200 ml), brine (1×200 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (3:2 40/60 petrol/Et_2O) gave the known[14] compound (**18**) (7.06 g, 73%) as a colourless oil: R_f 0.33 (1:1 40/60 petrol/Et_2O); δ_H(500 MHz; $CDCl_3$) 1.70 (3H, s), 1.75 (6H, s), 2.79 (2H, t, *J*=7.0 Hz), 4.06 (2H, d, *J*=6.0 Hz), 5.15–5.18 (1H, m), 5.43–5.46 (1H, m).

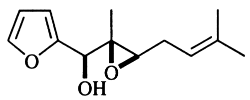


1.2.9. (2*S*,3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxirane-2-carbaldehyde (19).[15]

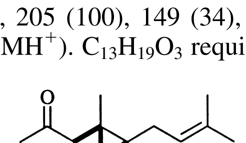
To a stirred suspension of powdered 4A molecular sieves (0.1 g) in dry DCM (5 ml) was added (−)-diethyl tartrate (61 μl, 0.36 mmol, 0.25 equiv.). The mixture was cooled to −22°C (dry ice/CCl_4), $Ti(OPr^i)_4$ (85 μl, 0.29 mmol, 0.2 equiv.) was added and the mixture stirred vigorously for 25 min. *tert*-Butylhydroperoxide (0.57 ml of a 5 M solution in decane, 2.85 mmol, 2.1 equiv.) was added, and stirring continued for 25 min. A solution of alcohol (**18**) (0.2 g, 1.43 mmol, 1.0 equiv.) in dry DCM (2 ml) was added, and after 30 min the mixture was placed in the freezer (−25°C) for 16 h. The mixture was diluted with Et_2O (15 ml), and filtered through a pad of Celite on top of a pad of silica, washing thoroughly with Et_2O. The filtrate was then concentrated. Purification by flash column chromatography (12:13 40/60 petrol/Et_2O) gave [(2*S*,3*R*)-3-((2*Z*)-3-methylbut-2-enyl)-2-methyloxiran-2-yl]methan-1-ol[2] (0.2 g, 90%, 98% ee) as a colourless oil: R_f 0.18 (1:1 40/60 petrol/Et_2O); $[\alpha]_D^{25}=12.9$ (*c*=1.5, $CHCl_3$) (lit.[15] 12.6 (*c*=2.13, $CHCl_3$); δ_H(250 MHz;

$CDCl_3$) 1.34 (3H, s), 1.67 (3H, s), 1.75 (3H, d, J=0.8 Hz), 2.15–2.26 (1H, m), 2.36–2.48 (1H, m), 3.07 (1H, t, J=6.5 Hz), 3.56–3.75 (2H, m), 5.15–5.22 (1H, m).

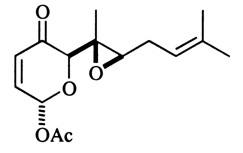
To a stirred solution of oxalyl chloride (1.67 g, 19.2 mmol, 2.0 equiv.) in dry DCM (20 ml) was added a solution of DMSO (2.72 ml, 58.4 mmol, 4.0 equiv.) in dry DCM (5 ml) dropwise at −78°C. After 10 min a solution of the alcohol (1.5 g, 9.6 mmol, 1.0 equiv.) in dry DCM (10 ml) was added dropwise. After 20 min Et_3N (10.7 ml, 76.8 mmol, 8.0 equiv.) was added, and the mixture allowed to warm up to rt. After 1 h the mixture was poured into H_2O (50 ml). The aqueous layer was extracted with DCM (2×40 ml), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (6:1 40/60 petrol/Et_2O) gave the title compound (1.2 g, 81%) as a colourless oil: R_f 0.32 (4:1 40/60 petrol/Et_2O); $[\alpha]_D^{25}=-51.9$ (c=1.01, CH_2Cl_2) (lit.[15] $[\alpha]_D^{25}=-52.2$ (c=0.985, CH_2Cl_2); δ_H(500 MHz; $CDCl_3$) 1.49 (3H, s), 1.71 (3H, s), 1.79 (3H, d, J=1.0 Hz), 2.28–3.33 (1H, m), 2.53–2.60 (1H, m), 3.20 (1H, t, J=6.5 Hz), 5.17–5.21 (1H, m), 8.90 (1H, s).



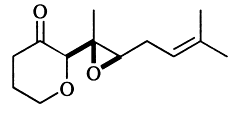
1.2.10. (1*R*)[(2*S*,3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl]-2-furylmethan-1-ol (20). To a stirred solution of furan (freshly distilled from $CaCO_3$, 2.27 ml, 31.17 mmol, 1.35 equiv.) in dry THF (40 ml) was added *n*BuLi (13.6 ml of a 2.3 M solution in hexane, 31.17 mmol, 1.35 equiv.) dropwise at −78°C. The mixture was stirred at −78°C for 20 min, at −5°C for 3 h, at rt for 10 min, and was then recooled to −78°C before a solution of aldehyde (**19**) (3.56 g, 23.09 mmol, 1.0 equiv.) in dry THF (8 ml) was added dropwise. The mixture was stirred at −78°C for 2 h, then allowed to warm to rt overnight. The mixture was quenched with sat. aq. NH_4Cl (50 ml). The layers were separated, and the aqueous layer extracted with Et_2O (3×30 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. ^1H NMR analysis of the crude product mixture indicated a 3.5:1 mixture of diastereomers. Purification by flash column chromatography (47:3 DCM:EtOAc) gave the title compound (3.02 g, 59%) as a pale yellow oil: R_f 0.30 (23:2 DCM:EtOAc); $[\alpha]_D^{25}=+29.3$ (c=1.04, $CHCl_3$) ν_{max}(film)/cm^{-1} 3430, 2916, 1674, 1385, 1052, 735; δ_H(400 MHz; $CDCl_3$) 1.25 (3H, s), 1.65 (3H, s), 1.74 (3H, s), 2.12–2.24 (1H, m), 2.36–2.44 (1H, m), 2.58 (1H, d, J=6.7 Hz), 3.15 (1H, t, J=6.5 Hz), 4.49 (1H, d, J=6.7 Hz), 5.14–5.19 (1H, m), 6.32–6.38 (2H, m), 7.39–7.40 (1H, m); δ_C(100 MHz; $CDCl_3$) 12.57, 17.93, 25.70, 27.27, 60.13, 62.37, 71.62, 107.14, 110.22, 118.33, 134.64, 142.15, 153.43; m/z (CI) 223 (27%, MH^+), 205 (100), 149 (34), 125 (43); HRMS: Found 223.1332 (MH^+). $C_{13}H_{19}O_3$ requires 223.1334.



1.2.11. 2-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](6*S*,2*R*)-6-hydroxy-6-hydro-2*H*-pyran-3-one (21). To a stirred solution of furan (**20**) (7.50 g, 33.7 mmol, 1.0 equiv.) in dry DCM (250 ml) was added $VO(acac)_2$ (1.18 g, 3.37 mmol, 0.1 equiv.) and *tert*-butylhydroperoxide (9.44 ml of a 5 M solution in decane, 47.2 mmol, 1.4 equiv.) at rt. After 2.5 h, the mixture was concentrated; the residue was dissolved in Et_2O and filtered through a pad of Florisil. The filtrate was concentrated, dissolved in the minimum amount of Et_2O and passed through a pad of silica (6 cm length), eluting with Et_2O. The filtrate was concentrated to afford the title compound (4.02 g, 51%) as an orange oil, which was used without purification in the next step: R_f 0.26 (22:3 DCM:EtOAc).

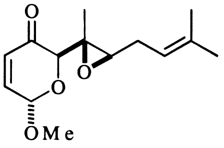


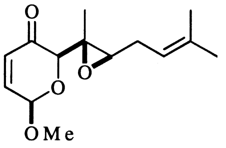
1.2.12. 6-[3-((2*E*)-3-Methylbut-2-enyl)(3*R*)-2-methyloxiran-2-yl](2*R*,6*R*)-5-oxo-6-hydro-2*H*-pyran-2-yl acetate (22α). To a stirred solution of pyranone (**21**) (1.397 g, 5.86 mmol, 1.0 equiv.) in dry DCM (20 ml) was added pyridine (3.8 ml, 46.90 mmol, 8.0 equiv.), acetic anhydride (2.8 ml, 29.31 mmol, 5.0 equiv.) and DMAP (1.1 mg) at 0°C. After 90 min H_2O (30 ml) was added. The layers were separated, and the aqueous layer extracted with DCM (3×20 ml). The combined organic layers were washed with brine (1×20 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (27:23 40/60 petrol/Et_2O) gave the title compound (1.117 mg, 68%) as a pale yellow oil: R_f 0.29 (1:1 40/60 petrol/Et_2O); $[\alpha]_D^{25}=+18.7$ (c=0.78, $CHCl_3$); ν_{max}(film)/cm^{-1} 2979, 1756, 1698, 1635, 1370, 1213, 948; δ_H(500 MHz; $CDCl_3$) 1.30 (3H, s), 1.67 (3H, s), 1.77 (3H, s), 2.13 (3H, s), 2.30–2.39 (2H, m), 3.01 (1H, t, J=6.5 Hz), 4.12 (1H, s), 5.28–5.31 (1H, m), 6.27 (1H, d, J=10.5 Hz), 6.61 (1H, d, J=3.5 Hz), 6.96 (1H, dd, J=10.5, 3.5 Hz); δ_C(125 MHz; $CDCl_3$) 12.6, 18.4, 21.3, 26.1, 27.4, 60.4, 61.4, 82.3, 87.2, 118.8, 128.9, 135.0, 142.7, 169.7, 193.0; m/z (CI) 263 (20%), 221 (100, $[M-OAc]^+$), 203 (28), 125 (23).



1.2.13. 2-[3-((2*E*)-3-Methylbut-2-enyl)(3*R*)-2-methyloxiran-2-yl](2*R*)-4,5,6-trihydro-2*H*-pyran-3-one (26). To a stirred solution of acetate (**22α**) (30 mg, 0.11 mmol, 1.0 equiv.) in THF (3 ml) was added Raney-Ni (130 mg of a suspension in water) in one portion at rt. After 5 h the mixture was diluted with Et_2O (10 ml) and filtered through a pad of silica, washing with Et_2O. The filtrate was then concentrated. Purification by flash column chromatography (DCM) gave the title compound (16 mg, 67%) as a pale yellow oil: R_f 0.17 (DCM); $[\alpha]_D^{25}=+8.04$ (c=0.95, $CHCl_3$); ν_{max}(film)/cm^{-1} 2926, 1723, 1449, 1384, 1090; δ_H(500 MHz; $CDCl_3$) 1.58 (3H, s), 1.94 (3H, s), 2.04 (3H, s), 2.34–2.36 (1H, m), 2.43–2.56 (2H, m), 2.65–2.76 (2H, m), 2.84–2.92 (1H, m), 3.20 (1H, t, J=6.5 Hz), 3.79 (1H, s), 3.99–4.04 (1H, m), 4.42–4.45 (1H, m), 5.53–5.56 (1H, m); δ_C(125 MHz; $CDCl_3$) 13.2, 18.4, 26.2, 27.5, 30.8, 38.6, 60.8, 60.9, 66.1, 88.6, 119.0, 134.9, 206.9; *m/z* (APCI) 225 (17%, MH$^+$), 207 (75), 149 (100), 125 (53); HRMS: Found 225.1495 (MH$^+$). $C_{13}H_{21}O_3$ requires 225.1491.

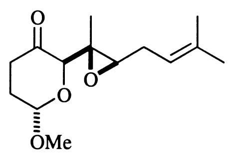
1.2.14. 2-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](6*S*,2*R*)-6-methoxy-6-hydro-2*H*-pyran-3-one (24α) and 2-[(3*R*)-3-((2*Z*)-3-methylbut-2-enyl)-2-methyloxiran-2-yl](2*R*,6*R*)-6-methoxy-6-hydro-2*H*-pyran-3-one (24β). To a stirred solution of the crude pyranone (**21**) (75 mg, 0.32 mmol, 1.0 equiv.) in MeI (3 ml) was added Ag_2O (375 mg, 1.57 mmol, 5.0 equiv.) in one portion a rt. The mixture was stirred in the dark for 40 h, diluted with Et_2O (15 ml), filtered through a pad of silica and concentrated. Purification by flash column chromatography (16:9 40/60 petrol/Et_2O) gave the desired products (21α) (30 mg, 38%) followed by compound (**21β**) (37 mg, 46%).



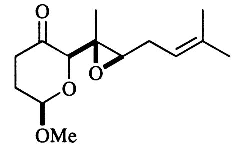


Data for compound (**24α**): R_f 0.30 (2:1 40/60 petrol/Et_2O); $[\alpha]_D^{25}=+33.1$ (c=1.21, $CHCl_3$); ν_{max}(film)/cm^{-1} 2930, 1698, 1633, 1453, 1049; δ_H(400 MHz; $CDCl_3$) 1.29 (3H, s), 1.66 (3H, s), 1.76 (3H, d, J=0.9 Hz), 2.31–2.36 (2H, m), 2.97 (1H, t, J=6.4 Hz), 3.53 (3H, s), 3.99 (1H, s), 5.19 (1H, d, J=3.5 Hz), 5.27–5.32 (1H, m), 6.09 (1H, d, J=10.3 Hz), 6.89 (1H, dd, J=10.3, 3.5 Hz); δ_C(100 MHz; $CDCl_3$) 12.14, 17.96, 25.73, 27.04, 56.71, 59.96, 61.27, 80.24, 93.94, 118.49, 127.63, 134.51, 143.81, 193.71; *m/z* (CI) 253 (48%, MH$^+$), 235 (83), 221 (83), 125 (100), 103 (91); HRMS: Found 253.1440 (MH$^+$). $C_{14}H_{21}O_4$ requires 253.1440.

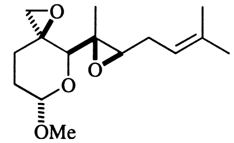
Data for compound (**24β**): R_f 0.22 (2:1 40/60 petrol/Et_2O); $[\alpha]_D^{25}=+27.5$ (c=0.97, $CHCl_3$); ν_{max}(film)/cm^{-1} 2932, 1698, 1628, 1389, 1209, 1058; δ_H(400 MHz; $CDCl_3$) 1.33 (3H, s), 1.65 (3H, s), 1.75 (3H, d, J=1.0 Hz), 2.28–2.39 (2H, m), 2.93 (1H, t, J=6.4 Hz), 3.60 (3H, s), 3.67 (1H, s), 5.26–5.31 (2H, m), 6.14 (1H, dd, J=10.4, 1.7 Hz), 6.90 (1H, dd, J=10.4, 1.4 Hz); δ_C(100 MHz; $CDCl_3$) 12.68, 18.42, 26.18, 27.51, 56.92, 60.54, 61.66, 85.03, 97.56, 118.91, 129.79, 134.9, 148.30, 193.63; *m/z* (CI) 253 (6%, MH$^+$), 235 (44), 221 (100), 125 (26); HRMS: Found 253.1440 (MH$^+$). $C_{14}H_{21}O_4$ requires 253.1440.



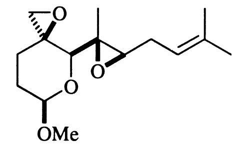
1.2.15. 2-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](6*S*,2*R*)-6-methoxy-4,5,6-trihydro-2*H*-pyran-3-one (28α). To a stirred solution of enone (**24α**) (425 mg, 1.69 mmol, 1.0 equiv.) in THF (7 ml) was added Raney-Ni (1.8 g of a suspension in water) in one portion at rt, and the mixture stirred for 3 h. The mixture was diluted with Et_2O (30 ml), filtered through a pad of silica and concentrated. Purification by flash column chromatography (5:3 30/40 petrol/Et_2O) gave the title compound (391 mg, 92%) as a colourless oil: R_f 0.29 (5:3 30/40 petrol/Et_2O); $[\alpha]_D^{25}=+18.2$ (c=1.01, $CHCl_3$); ν_{max}(film)/cm^{-1} 2916, 1728, 1676, 1450, 1055; δ_H(400 MHz; $CDCl_3$) 1.30 (3H, s), 1.65 (3H, s), 1.75 (3H, d, J=0.9 Hz), 1.94–2.02 (1H, m), 2.26–2.34 (3H, m), 2.40–2.56 (2H, m), 2.94 (1H, t, J=6.5 Hz), 3.44 (3H, s), 3.71 (1H, s), 4.97 (1H, t, J=4.3 Hz), 5.24–5.28 (1H, m); δ_C(100 MHz; $CDCl_3$) 12.51, 17.95, 25.73, 27.05, 28.55, 34.09, 55.29, 59.86, 60.81, 80.55, 97.36, 118.54, 134.47, 207.49; *m/z* (CI) 255 (18%, MH$^+$), 237, (46), 223 (100), 125 (91); HRMS: Found 255.1595 (MH$^+$). $C_{14}H_{23}O_4$ requires 255.1596.



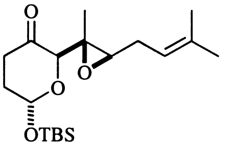
1.2.16. 2-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](2*R*,6*R*)-6-methoxy-4,5,6-trihydro-2*H*-pyran-3-one (28β). To a stirred solution of enone (**24β**) (804 mg, 3.19 mmol, 1.0 equiv.) in THF (15 ml) was added Raney-Ni (4.0 g of a suspension in water) in one portion at rt, and the mixture stirred for 3 h. The mixture was diluted with Et_2O (30 ml), filtered through a pad of silica and concentrated. Purification by flash column chromatography (5:3 30/40 petrol/Et_2O) gave the title compound (716 mg, 89%) as a colourless oil: R_f 0.15 (5:3 30/40 petrol/Et_2O); $[\alpha]_D^{25}=+16.6$ (c=0.89, $CHCl_3$); ν_{max}(film)/cm^{-1} 2967, 1727, 1451, 1386, 1054; δ_H(400 MHz; $CDCl_3$) 1.32 (3H, s), 1.65 (3H, s), 1.74 (3H, d, J=0.9 Hz), 2.10–2.18 (2H, m), 2.22–2.29 (1H, m), 2.32–2.42 (2H, m), 2.63 (1H, dt, J=17.2, 7.3 Hz), 2.86 (1H, t, J=6.4 Hz), 3.54 (3H, s), 3.57 (1H, s), 4.86–4.88 (1H, m), 5.23–5.27 (1H, m); δ_C(100 MHz; $CDCl_3$) 12.55, 17.94, 25.70, 27.08, 28.72, 34.33, 56.31, 60.09, 60.74, 85.00, 99.53, 118.45, 134.44, 206.47; *m/z* (CI) 255 (20%, MH$^+$), 237 (62), 223 (100), 205 (42), 125 (72); HRMS: Found 255.1597 (MH$^+$). $C_{14}H_{23}O_4$ requires 255.1596.

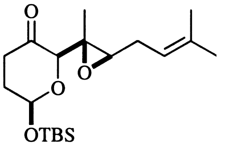


1.2.17. 4-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](3*S*,4*S*,6*S*)-6-methoxy-1,5-dioxaspiro[2.5]octane (30α). To a stirred solution of ketone (**28α**) (325 mg, 1.28 mmol, 1.0 equiv.) and dibromomethane (108 μl, 1.54 mmol, 1.2 equiv.) in dry THF (5 ml) was added *n*BuLi (0.63 ml of a 2.45 M solution in hexanes, 1.54 mmol, 1.2 equiv.) dropwise at −78°C. The mixture was stirred at −78°C for 2 h, then allowed to warm to rt over 16 h, then quenched with sat. aq. NH_4Cl (10 ml). The layers were separated, and the aqueous layer extracted with Et_2O (3×10 ml). The combined organic layers were dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (49:1 DCM:EtOAc) gave the title compound (282 mg, 82%) as a pale yellow oil: R_f 0.25 (16:9 40/60 petrol/EtOAc); $[\alpha]_D^{25}=+57.2$ (c=1.62, $CHCl_3$); ν_{max}(film)/cm^{-1} 2934, 1674, 1444, 1218, 1020, 965; δ_H(400 MHz; $CDCl_3$) 1.13–1.18 (1H, m), 1.42 (3H, s), 1.64 (3H, s), 1.76 (3H, d, J=1.0 Hz), 1.78–1.80 (1H, m), 2.06–2.14 (2H, m), 2.33–2.43 (2H, m), 2.52 (1H, d, *J*=4.4 Hz), 2.63–2.67 (1H, m), 2.81 (1H, d, *J*=4.4 Hz), 3.39 (3H, s), 3.57 (1H, s), 4.90 (1H, d, *J*=2.5 Hz), 5.14–5.18 (1H, m); δ_C(100 MHz; CDCl$_3$) 12.71, 17.96, 25.70, 26.85, 27.92, 50.07, 54.85, 56.45, 60.44, 75.59, 97.95, 118.03, 135.22; *m/z* (GCMS) 269 (4%, MH$^+$), 221 (23), 205 (50), 127 (100); HRMS: Found 269.1752 (MH$^+$). $C_{15}H_{25}O_4$ requires 269.1753



1.2.18. 4-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](3*S*,4*S*,6*R*)-6-methoxy-1,5-dioxaspiro[2.5]-octane (30β). To a stirred solution of ketone (**28β**) (630 mg, 2.48 mmol, 1.0 equiv.) and dibromomethane (0.19 ml, 2.73 mmol, 1.1 equiv.) in dry THF (10 ml) was added *n*BuLi (1.1 ml of a 2.45 M solution in hexanes, 2.73 mmol, 1.1 equiv.) dropwise at −78°C. The mixture was stirred at −78°C for 2 h, then allowed to warm to rt over 16 h, then quenched with sat. aq. NH$_4$Cl (10 ml). The layers were separated, and the aqueous layer extracted with Et$_2$O (3×10 ml). The combined organic layers were dried (MgSO$_4$), filtered and concentrated. Purification by flash column chromatography (3:2 40/60Petrol/Et$_2$O) gave the title compound (532 mg, 80%) as a pale yellow oil: R_f 0.11 (16:9 40/60 petrol/EtOAc); $[\alpha]_D^{25}=+42.6$ (*c*=1.0, CHCl$_3$); ν_{max}(film)/cm^{-1} 2934, 1673, 1450, 1380, 1041, 931; δ_H(400 MHz; CDCl$_3$) 1.33–1.39 (1H, m), 1.36 (3H, s), 1.65 (3H, s), 1.74 (3H, s), 1.85–1.89 (2H, m), 2.08–2.17 (2H, m), 2.39–2.46 (1H, m), 2.56 (1H, d, *J*=4.4 Hz), 2.66 (1H, dd, *J*=7.3, 5.7 Hz), 2.84 (1H, d, *J*=4.4 Hz), 3.30 (1H, s), 3.55 (3H, s), 4.49–4.52 (1H, m), 5.14–5.18 (1H, m); δ_C(100 MHz; CDCl$_3$) 12.74, 17.95, 25.70, 26.87, 29.30, 30.57, 49.55, 55.73, 56.30, 59.65, 60.36, 82.21, 102.72, 117.93, 135.48; *m/z* (APCI) 269 (18%, MH$^+$), 237 (69), 219 (24), 169 (21).



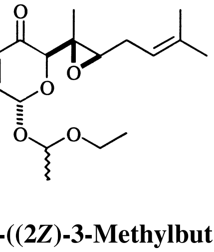


1.2.19. 2-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-methyloxiran-2-yl](2*R*,6*S*)-6-[((1,1-dimethyl)ethyl)dimethylsilyloxy]-4,5,6-trihydro-2*H*-pyran-3-one (27α) and 2-[(3*R*)-3-((2*Z*)-3-methylbut-2-enyl)-methyloxiran-2-yl](2*R*,6*R*)-6-[((1,1-dimethyl)ethyl)dimethylsilyloxy]-4,5,6-trihydro-2*H*-pyran-3-one (27β). To a stirred solution of alcohol (**21**) (500 mg, 2.1 mmol, 1.0 equiv.) in dry DCM (6 ml) was added imidazole (429 mg, 6.3 mmol, 3.0 equiv.) and TBSCl (633 mg, 4.2 mmol, 2.0 equiv.) at rt. After 2 h the mixture was partitioned between DCM (10 ml) and H$_2$O (15 ml). The aqueous layer was extracted with DCM (2×10 ml), and the combined organic layers were washed with brine (1×15 ml), dried (MgSO$_4$), filtered and concentrated to afford a yellow oil, which was used without further purification in the next step: *m/z* (CI) 353 (35%, MH$^+$), 335 (34), 221 (100), 211 (46), 127 (37); HRMS: Found 353.2145 (MH$^+$). $C_{19}H_{33}O_4Si$ requires 353.2148.

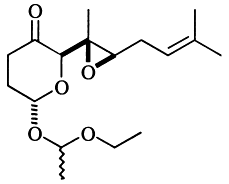
To a stirred solution of the crude enone in THF (10 ml) was added Raney-Ni (2.5 g of a suspension in H$_2$O) in one portion at rt. After 4 h the mixture was diluted with Et$_2$O (30 ml), filtered through a pad of silica and concentrated. Purification by flash column chromatography (22:3 40/60 petrol/Et$_2$O) gave the desired products (**27α**) (171 mg, 23%) followed by (**27β**) (367 mg, 49%) as colourless oils.

Data for compound (**27α**): R_f 0.28 (22:3 40/60 petrol/Et$_2$O); $[\alpha]_D^{25}=+91.9$ (*c*=1.05, CHCl$_3$); ν_{max}(film)/cm^{-1} 2930, 1728, 1463, 1254, 1047; δ_H(500 MHz; CDCl$_3$) 0.19 (6H, s), 0.94 (9H, s), 1.32 (3H, s), 1.70 (3H, s), 1.79 (3H, d, *J*=0.5 Hz), 1.98–2.04 (1H, m), 2.27–2.32 (2H, m), 2.38–2.47 (2H, m), 2.64–2.68 (1H, m), 2.98 (1H, t, *J*=6.5 Hz), 3.92 (1H, s), 5.29–5.32 (1H, m), 5.49 (1H, t, *J*=3.5 Hz); δ_C(125 MHz; CDCl$_3$) −5.1, −4.0, 13.4, 18.4, 26.1, 26.2, 27.6, 31.9, 34.3, 60.3, 60.8, 81.0, 91.6, 119.1, 134.7, 207.9; *m/z* and HRMS: molecular ions could not be found under any ionisation conditions.

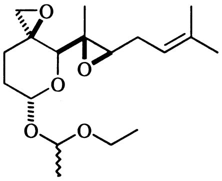
Data for compound (**27β**): R_f 0.16 (22:3 40/60 petrol/Et$_2$O); $[\alpha]_D^{25}=+11.5$ (*c*=1.3, CHCl$_3$); ν_{max}(film)/cm^{-1} 2957, 1731, 1676, 1387, 1175, 1056, 839; δH(500 MHz; CDCl$_3$) 0.20 (3H, s), 0.21 (3H, s), 0.95 (9H, s), 1.36 (3H, s), 1.69 (3H, s), 1.79 (3H, d, *J*=1.0 Hz), 2.11–2.22 (2H, m), 2.28–3.35 (1H, m), 2.38–2.45 (2H, m), 2.67 (1H, dt, *J*=17.0, 6.5 Hz), 2.89 (1H, t, *J*=6.5 Hz), 3.58 (1H, s), 5.29–5.35 (2H, m); δ_C(125 MHz, CDCl$_3$) −4.7, −3.6, 13.1, 18.4, 26.2, 27.5, 32.3, 35.2, 60.4, 61.1, 85.8, 94.4, 119.0, 134.8, 206.7; *m/z* and HRMS: molecular ions could not be found under any ionisation conditions.



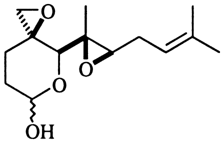
1.2.20. 2-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](6*S*,2*R*)-6-((1-ethoxyethyl)ethyl)-6-hydro-2*H*-pyran-3-one (25α). To a stirred solution of crude alcohol (**21**) (100 mg, 0.42 mmol, 1.0 equiv.) in dry DCM (4 ml) was added ethyl vinyl ether (0.9 ml, 9.4 mmol, 22.5 equiv.) and PPTS (ca. 10 mg) at 0°C. The mixture was warmed to rt, stirred for 4 h, then partitioned between DCM (10 ml) and sat. aq. NaHCO$_3$ (15 ml). The aqueous layer was extracted with DCM (3×10 ml), and the combined organic layers were dried (MgSO$_4$), filtered and concentrated. Purification by flash column chromatography (18:7 40/60 petrol/Et$_2$O) gave the title compound (69 mg, 53%) as a colourless oil (ca. 1:1 mixture of diastereomers): R_f 0.28 (1:1 40/60 petrol/Et$_2$O); $[\alpha]_D^{25}=+5.9$ (*c*=0.39, CHCl$_3$); ν_{max}(film)/cm^{-1} 2980, 1698, 1632, 1385, 1009, 877; δ_H(250 MHz; CDCl$_3$) 1.19–1.25 (6H, m), 1.27 (6H, s), 1.37 (3H, d, *J*=5.3 Hz), 1.43 (3H, d, *J*=5.4 Hz), 1.65(6H, s), 1.75 (6H, d, *J*=0.8 Hz), 2.27–2.38 (4H, m), 2.94 (2H, t, *J*=6.4 Hz), 3.46–3.60 (2H, m), 3.68–3.82 (2H, m), 3.99 (1H, s), 4.11 (1H, s), 4.97 (1H, q, *J*=5.4 Hz), 5.05 (1H, q, *J*=5.3 Hz), 5.26–5.32 (2H, m), 5.57 (1H, d, *J*=3.6 Hz), 5.61 (1H, d, *J*=3.6 Hz), 6.07 (1H, d, *J*=10.2 Hz), 6.11 (1H, d, *J*=10.2 Hz), 6.82 (1H, dd, *J*=10.2, 3.6 Hz), 6.89 (1H, dd, *J*=10.2, 3.6 Hz); δ_C(63 MHz; CDCl$_3$) 12.54, 12.65, 15.58, 15.69, 18.36, 21.31, 21.43, 26.13, 27.48, 27.52, 60.19, 60.27, 61.42, 61.62,.62.48, 63.94, 80.88, 80.90, 88.74, 90.06, 118.96, 127.77, 128.05, 134.76, 134.85, 144.43, 144.87, 193.97, 194.21; *m/z* (CI) 328 (7%, MNH_4^+), 311 (12, MH^+), 293 (66), 267 (51), 221 (100), 125 (37); HRMS: Found 311.1850 (MH^+). $\text{C}_{17}\text{H}_{27}\text{O}_5$ requires 311.1858.



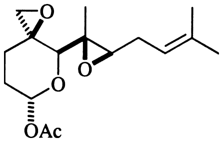
1.2.21. 2-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](6*S*,2*R*)-6-((1-ethoxy)ethyl)-4,5,6-trihydro-2*H*-pyran-3-one (29α). To a stirred solution of enone (**25α**) (67 mg, 0.22 mmol, 1.0 equiv.) in THF (3 ml) was added Raney-Ni (300 mg of a suspension in H_2O) in one portion at rt, and the mixture stirred for 3 h. The mixture was diluted with Et_2O (10 ml), filtered through silica, and concentrated. Purification by flash column chromatography (18:7 40/60 petrol/Et_2O) gave the title compound (62 mg, 92%) as a pale yellow oil; R_f 0.20 (2:1 40/60 petrol/Et_2O); $[\alpha]_\text{D}^{25}=+153.9$ (c=0.41, CHCl_3); ν_max(film)/cm^{-1} 2978, 1732, 1675, 1380, 1142, 860; δ_H(250 MHz; CDCl_3) 1.16–1.26 (6H, m), 1.28 (6H, s), 1.35 (3H, d, J=5.3 Hz), 1.39 (3H, d, J=5.3 Hz), 1.65 (6H, s), 1.75 (6H, s), 1.91–2.08 (2H, m), 2.20–2.42 (6H, m), 2.45–2.62 (4H, m), 2.92 (1H, t, J=6.4 Hz), 2.93 (1H, t, J=6.4 Hz), 3.48–3.57 (2H, m), 3.66–3.82 (2H, m), 3.77 (1H, s), 3.89 (1H, s), 4.94 (1H, q, J=5.3 Hz), 5.00 (1H, q, J=5.3 Hz), 5.22–5.28 (2H, m), 5.33 (1H, t, J=4.8 Hz), 5.39 (1H, t, J=4.7 Hz); δ_C(63 MHz; CDCl_3) 12.89, 13.30, 15.61, 15.70, 18.36, 21.36, 21.54, 26.14, 27.47, 28.71, 29.15, 34.51, 34.62, 60.17, 60.20, 60.97, 61.18, 62.40, 63.86, 81.32, 92.45, 93.82, 98.72, 99.81, 118.95, 134.78, 134.85, 207.82, 208.09; *m/z* (CI) 330 (7%, MNH_4^+), 313 (8, MH^+), 295 (100), 223 (58), 73 (32); HRMS: Found 313.2011 (MH_+). $\text{C}_{17}\text{H}_{29}\text{O}_5$ requires 313.2015.



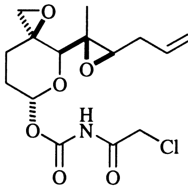
1.2.22. 4-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](3*S*,4*S*,6*S*)-6-((1-ethoxy)ethyl)-1,5-dioxaspiro[2.5]octane (31α). To a stirred solution of ketone (**29α**) (61 mg, 0.2 mmol, 1.0 equiv.) and dibromomethane (19 μl, 0.26 mmol, 1.35 equiv.) in dry THF (3 ml) was added *n*BuLi (110 μl of a 2.4 M solution in hexanes, 0.26 mmol, 1.35 equiv.) dropwise at −78°C. The mixture was stirred at −78°C for 2 h, then allowed to warm to rt over 16 h, then quenched with sat. aq. NH_4Cl (10 ml). Et_2O (10 ml) was added, the layers were separated, and the aqueous layer extracted with Et_2O (3×10 ml). The combined organic layers were dried (MgSO_4), filtered and concentrated. Purification by flash column chromatography (18:7 40/60Petrol/Et_2O) gave the title compound (50 mg, 79%) as a pale yellow oil: R_f 0.33 (2:1 40/60 petrol/EtOAc); $[\alpha]_\text{D}^{25}=+58.5$ (c=0.395, CHCl_3); ν_max(film)/cm^{-1} 2977, 2934, 1673, 1381, 1133, 973; δ_H(250 MHz; CDCl_3) 1.21 (3H, t, J=7.0 Hz), 1.22 (3H, t, J=7.1 Hz), 1.31 (6H, s), 1.36 (3H, d, J=5.2 Hz), 1.37 (3H, d, J=5.3 Hz), 1.65 (6H, s), 1.75 (6H, s), 1.81–2.00 (2H, m), 2.03–2.22 (4H, m), 2.35–2.50 (4H, m), 2.53 (2H, d, J=4.4 Hz), 2.6–2.68 (2H, m), 2.82 (1H, d, J=4.4 Hz), 2.83 (1H, d, J=4.4 Hz), 2.95–3.06 (2H, m), 3.42–3.68 (2H, m), 3.63 (1H, s), 3.65–3.91 (2H, m), 3.78 (1H, s), 4.87–4.98 (2H, m), 5.16 (2H, t, J=7.4 Hz), 5.24 (1H, d, J=1.9 Hz), 5.29 (1H, d, J=2.1 Hz); δ_C(63 MHz; CDCl_3) 13.15, 13.18, 15.68, 18.35, 21.23, 21.87, 21.13, 27.23, 27.25, 27.38, 28.23, 28.95, 50.59, 50.65, 56.94, 57.02, 59.82, 59.86, 60.68, 60.80, 62.66, 64.07, 76.47, 76.56, 92.78, 95.14, 99.08, 99.53, 118.47, 135.60, 135.64; *m/z* (CI) 344 (6%, MNH_4^+), 281 (9), 237 (82), 219 (23), 73 (100).



1.2.23. 4-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](3*S*,4*S*)-1,5-dioxaspiro[2.5]octan-6-ol (32). To a stirred solution of epoxide (**31α**) (19.5 mg, 0.06 mmol) in 4:1 acetone/water (1.5 ml) was added PPTS (ca. 3 mg) at 45°C. After 90 min more PPTS (ca. 3 mg) and solvent (0.5 ml) were added, and the mixture stirred for another 90 min. The mixture was then partitioned between EtOAc (10 ml) and sat. aq. NaHCO_3 (10 ml). The aqueous layer was extracted with EtOAc (3×10 ml), and the combined organic layers were dried (MgSO_4), filtered and concentrated to afford the crude product (13 mg, 85%) as a yellow oil, which was used without further purification in the next step: R_f 0.21 (40/60 petrol/EtOAc).



1.2.24. 4-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](3*S*,4*S*,6*R*)-1,5-dioxaspiro[2.5]oct-6-yl acetate (33α). To a stirred solution of the crude lactol (**32**) (12 mg, 0.05 mmol, 1.0 equiv.) in dry DCM (4 ml) was added pyridine (38 μl, 0.5 mmol, 10.0 equiv.), Ac_2O (35 μl, 0.4 mmol, 8.0 equiv.) and DMAP (9 mg, 0.08 mmol, 1.5 equiv.) at 0°C. The mixture was allowed to warm to rt over 2 h, then partitioned between DCM (10 ml) and H_2O (10 ml). The aqueous layer was extracted with DCM (3×10 ml), and the combined organic layers were dried (MgSO_4), filtered and concentrated. Purification by flash column chromatography (12:13 40/60 petrol/Et_2O) gave the title compound (10 mg, 72%) as a colourless oil: R_f 0.25 (2:3 40/60 petrol/Et_2O); $[\alpha]_\text{D}^{25}=+26.4$ (c=0.315, CHCl_3); ν_max(film)/cm^{-1} 2964, 2933, 1749, 1673, 1372, 1204, 1008, 945; δ_H(500 MHz; CDCl_3) 1.34 (1H, dt, J=13.6, 4.0 Hz), 1.37 (3H, s), 1.71 (3H, s), 1.80 (3H, s), 1.89–1.1.93 (1H, m), 2.14 (3H, s), 2.14–2.19 (1H, m), 2.28 (1H, ddt, J=13.6, 4.0, 4.0 Hz), 2.40 (1H, dt, J=13.5, 4.5 Hz), 2.45–2.50 (1H, m), 2.62 (1H, d, J=4.4 Hz), 2.72 (1H, dd, J=7.3, 5.7 Hz), 2.92 (1H, d, J=4.4 Hz), 3.76 (1H, s), 5.22 (1H, t J=7.5 Hz), 6.40 (1H, s); δ_C(125 MHz; $CDCl_3$) 13.02, 18.38, 21.62, 26.13, 26.87, 27.33, 27.41, 50.71, 56.41, 59.74, 60.59, 78.69, 92.35, 118.42, 135.80, 169.77; m/z (CI) 314 (17%, MNH_4^+), 297 (7, MH_+), 237 (100), 219 (62), 177 (36), 125 (48); HRMS: Found 314.1966 (MNH_4^+). $C_{16}H_{28}NO_5$ requires 314.1967.



1.2.25. {4-[(3*R*)-3-((2*Z*)-3-Methylbut-2-enyl)-2-methyloxiran-2-yl](3*S*,4*S*,6*R*)-1,5-dioxaspiro[2.5]oct-6-yloxy}-N-(2-chloroacetyl)carboxamide (34α). To a stirred solution of the crude lactol (**32**) (88 mg, 0.35 mmol, 1.0 equiv.) in dry DCM (4 ml) was added chloroacetyl isocyanate (60 μl, 0.7 mmol, 2.0 equiv.) dropwise at 0°C. After 70 min at 0°C the mixture was partitioned between EtOAc (15 ml) and H_2O (15 ml). The aqueous layer was extracted with EtOAc (3×10 ml), and the combined organic layers were washed with brine (1×15 ml), dried ($MgSO_4$), filtered and concentrated. Purification by flash column chromatography (14:11 40/60 petrol/EtOAc) gave the title compound (82 mg, 64%) as a colourless paste: R_f 0.32 (1:1 40/60 petrol/EtOAc); $[\alpha]_D^{25}=+20.4$ (c=0.28, $CHCl_3$); δ_H(500 MHz; $CDCl_3$) 1.29 (3H, s), 1.63 (3H, s), 1.72 (3H, s), 1.90–1.94 (1H, m), 2.03–2.11 (2H, m), 2.21–2.28 (1H, m), 2.39 (2H, dt, J=13.7, 4.6 Hz), 2.58 (1H, d, J=4.3 Hz), 2.65 (1H, dd, J=7.3, 5.7 Hz), 2.85 (1H, d, J=4.3 Hz), 3.72 (1H, s), 4.50 (2H, s), 5.11–5.14 (1H, m), 6.33 (1H, s), 8.62 (1H, br s); δ_C(125 MHz; $CDCl_3$) 12.39, 17.86, 25.57, 26.01, 26.72, 43.80, 50.15, 55.65, 59.29, 60.21, 78.46, 94.31, 117.59, 135.58, 150.01, 167.16, 200.42; m/z (CI) 393 (3%, MNH_4^+, ^{37}Cl), 391 (10, MNH_4^+, ^{35}Cl), 331 (9), 237 (43), 219 (25), 95 (100).

Acknowledgements

We thank Dr R. M. Adlington for fruitful discussions. P. G. B. also thanks the EPSRC for a graduate fellowship.

References

1. (a) Elbe, T. E.; Hanson, F. R. *Antibiot. Chemother.* **1951**, *1*, 54. (b) McCorkindale, N. J.; Sime, J. G. *Proc. Chem. Soc.* **1961**, 331.
2. (a) Ingber, D.; Fujita, T.; Kishimoto, S.; Sudo, K.; Kanamaru, T.; Brem, H.; Folkman, J. *Nature* **1990**, *348*, 555. (b) Folkman, J. *Nature Med.* **1995**, *1*, 27.
3. Liekens, S.; DeClercq, E.; Neyts, J. *Biochem. Pharmacol.* **2001**, *61*, 253.
4. (a) Han, C. K.; Ahn, S. K.; Choi, N. S.; Hong, R. K.; Moon, S. K.; Chun, H. S.; Lee, S. J.; Kim, J. W.; Hong, C. I.; Kim, D.; Yoon, J. K.; No, K. T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 39. (b) Marui, S.; Yamamoto, T.; Sudo, K.; Akimoto, H.; Kishimoto, S. *Chem. Pharm. Bull.* **1995**, *43*, 588. (c) Bond, S. J.; Klein, S. A.; Anderson, G. L.; Wittliff, J. L. *J. Surg. Res.* **1999**, *82*, 268. (d) Bowder, T.; Butterfield, C. E.; Kraeling, B. M.; Shi, B.; Marshall, B.; O'Reilly, M. S.; Folkman, J. *Cancer Res.* **2000**, *60*, 1878. (e) Hasuike, T.; Hino, M.; Yamamune, T.; Nishikawa, Y.; Morii, H.; Tatsumi, N. *Eur. J. Haematol.* **1997**, *58*, 293.
5. (a) Taunton, J. *Chem. Biol.* **1997**, *4*, 493. (b) Borman, S. *Chem. Eng. News* **1997**, *16*, 39. (c) Hawkins, M. J. *Curr. Opin. Oncol.* **1995**, *7*, 90. (d) Twardowski, P.; Gradishar, W. J. *Curr. Opin. Oncol.* **1997**, *9*, 584.
6. Dai, X. B.; Griffith, E. C.; Liu, J. O. Abstracts of Papers. *219th National Meeting of the American Chemical Society, San Francisco, CA*; American Chemical Society: Washington, DC, 2000 MEDI-061.
7. Lowther, W. T.; McMillen, D. A.; Orville, A. M.; Matthews, B. W. *Proc. Natl Acad. USA* **1998**, *95*, 12153.
8. Liu, S.; Widom, J.; Kemp, C. W.; Crews, C. M.; Clardy, J. *Science* **1998**, *282*, 1324.
9. Sammes, P. G.; Street, L. J.; Kirby, P. *J. Chem. Soc. Perkin Trans. 1* **1983** (11), 2729.
10. Pirrung, M. C.; Webster, N. J. G. *J. Org. Chem.* **1987**, *52*, 3603.
11. Martin, S. F.; Zinke, P. W. *J. Am. Chem. Soc* **1989**, *111*, 2311.
12. Taber, D. F.; Christos, T. E.; Rheinhold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1999**, *121*, 5589.
13. Michnick, T. J.; Matteson, D. S. *Synlett* **1991**, 631.
14. Mori, K.; Ueda, H. *Tetrahedron* **1981**, *37*, 2581.
15. Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, *117*, 7379–7384.
16. Barrero, A. F.; Alvarez-Manzaneda, E. J.; Charboun, R.; Meneses, R. *Synlett* **1999**, 1663.